**In the claims:**

Please amend claims 1, 3 and 4 as shown on the attached "Claim Sheets Marked up to Show Changes".

Please add new claims 23 to 44 as shown in the attached "Clean Claim Sheets" which shows all claims pending in the application, after entry of this amendment.

## REMARKS

Enclosed herewith is a petition for a three month extension of time, pursuant to 37 C.F.R. §1.136 (a) and an authorization to charge the appropriate fee to our Deposit Account No. 12-2475. Upon granting this petition, the deadline for filing a timely response will be extended up to and including March 13, 2001.

Claims 1, 3 and 4 have been amended to correct informalities. Claims 23 – 44 have been added. These amendments add no new matter, are fully supported by the application as filed, are not related to issues of patentability and, therefore, should not be construed as limiting the appropriate scope of protection provided under the doctrine of equivalents.

Applicant responds below to each of the objections and/or rejections raised in the non-final Office Action mailed September 13, 2000.

### I. The Section 112, First Paragraph, Rejection on Insufficient Description Grounds of Paragraph 5, Pages 2 to 3

Claims 1 to 4 and 6 stand rejected under 35 USC §112, first paragraph as allegedly failing to provide adequate written description of the claimed invention.

In support of the present rejection, the Examiner states:

> "The instant claims encompass bridge molecules that bind to costimulatory molecules other than CD28, 4-1BB, and CTLA-4. The instant claims also encompass bridge molecules that are not limited to bispecific monoclonal antibodies and tumor cells that are not limited to hepatocellular carcinoma cells and colon carcinoma cells. There is insufficient disclosure in the specification on said composition and the components of said composition." Office Action mailed September 13, 2000, page 3.

Applicant respectfully traverses the present rejection. Applicant submits that the claims comply with the written description requirement. Applicant notes that under the new written description guidelines, as published in the *Federal Register*, Vol. 66, No.4,

> "[t]here is a strong presumption that an adequate written description of the claimed invention is present in the specification as filed... Consequently, rejection of an original claim for lack of written description should be rare." *Id.* at Section II A., p. 1105.

The new guidelines further describe that the "written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice." *Id.* at Section II A (3) a (2). In the instant case, Applicant has supplied sufficient description, by providing the complete acts and/or processes necessary for an actual reduction to practice, of a representative number of species including, as the Examiner notes, human clinical data on human hepatocellular carinoma and colon cancer. Page 3.

The Examiner acknowledges that the specification discloses a number of binding sites, for costimulatory molecules on the surface of T cells, including biding sites for CD28, 4-1BB, CTLA-4 or ICAM-1, ICAM-2, ICAM-3, LFA-1, LFA-2, VLA-1, VCAM-1, B7-1, B7-2 and other cell adhesion proteins, as well as, other cell surface proteins capable of activating T cell costimulatory pathways through T cell surface proteins, antigens, fatty acids, lipids, steroids and sugars. The Examiner further acknowledges that the specification describes a number of bridge molecules that

may include bispecific monoclonal antibodies, fusion proteins, organic polymers and various hybrids, and that the specification describes the procedure of the instant claims as practiced for such target diseased cells as hepatoma tumor cells, lymphoma cells and colon cancer cells, as evidenced by examples 2, 7, 8 and 16. Hence, Applicant contends that the specification does convey, to the artisan of ordinary skill in the field, that the Applicant did indeed have possession, at the time of invention, of a representative number of species of the claimed immunogenic composition comprising autologous target diseased cells and bridge molecules capable of stimulating T cell activation comprising one or more binding sites for one or more costimulatory molecules on the surface of T cells.

Applicant notes that as stated in the new guidelines, an adequate written description may be shown by any description of sufficient relevant, identifying characteristics so long as a person skilled in the art would recognize that the inventor had possession of the claimed invention. *Id.* at II A 3 (a). To this extant, the burden of proof for establishing a *prima facie case* of inadequate written description must include the reasons "why a person skilled in the art at the time the application was filed would not have recognized that the inventor was in possession of the invention as claimed in view of the disclosure of the application as filed;" keeping in mind that a "general allegation of 'unpredictability in the art' is not sufficient reason to support a rejection for lack of adequate written description." *Id.* at III A (2).

In view of the above, applicant respectfully asks the Examiner withdraw the rejection, or in the alternative, to point out with particularity why, given the teachings in the specification as filed (particularly examples 2, 7, 8 and 16), an artisan of ordinary skill in the art would not have recognized that the inventor was in possession of the claimed genus. Should the present rejection be maintained, Applicant requests further clarification of the Examiner's rationale for this rejection.

## II. The Section 112, First Paragraph, Rejection on Non-enablement Grounds of Paragraph 6, Pages 4 to 5

Claims 1-4 and 6 stand rejected under 35 USC §112, first paragraph, because the specification allegedly does not provide enablement for the claimed composition and claimed vaccine.

The Examiner states:

> "The specification provides no guidance as to which of the numerous combinations of the disclosed substances can serve as binding sites for costimulatory molecules, or can serve as bridge molecules, and what combinations can be used to "arm" any particular tumor cell." Office Action mailed September 13, 2000, page 5.

Further, the Examiner states that:

> "The state of the art is such that it is unpredictable in the absence of appropriate evidence whether the claimed compositions can be used as vaccines or for the treatment of any diseased mammal having any diseased cells. Because of this lack of guidance, the extended experimentation that would be required to determine which substances would be suitable components for the claimed composition/vaccine...and due to the difficulty in predicting whether therapeutic success in relying upon increasing CTL responses for anti-tumor therapy will be achieved; even if a significant increase in anti-tumor CTL is obtained by immunization, it would require undue experimentation for one of skill in the art to arrive at other components for said composition/vaccine and to use said composition/vaccine." Office Action mailed September 13, 2000, page 5.

Applicant respectfully traverses this rejection. Applicant submits that the claims enable the disclosed invention. It is well settled, that patent applicants are not required to disclose and test every species that may be encompassed by their claims, even in an unpredictable art. *In re Angstadt*, 537 F.2d 498, 502-03, 190 USPQ 214, 218 (CCPA 1976). Indeed, it is not even required that every embodiment in a disclosure be operative in order to be enabling under 35 USC 112, first paragraph.

*Atlas Powder Co. v. E.I. Dupont de Nemours & Co.*, 750 F.2d 1569, 224 USPQ 409 (Fed. Cir. 1984). As held by *In re Fuetterer*, 138 USPQ 217 (CCPA 1963), patent applicants must be able to obtain claims that adequately protect their inventions, even though some experimentation may be required to determine if a product of method falls within the scope of the claim.

Since all that is required in order to enable a claimed invention, is to provide sufficient information that one skilled in the art can make and use the claimed invention, Applicant contends that he has supplied sufficient information, such that one skilled in the art can make and use the claimed invention. The Examiner acknowledges that the specification is enabling for representative compositions comprising

1) a hep 1-6 tumor cell and anti-CD28 Bi-Mabs comprising gp55, gp 115, gp 95, gp 210, or

2) CD28:gp55 armed hepa 1-6 cells, EL-4 cells or SMCC-1 cells, or

2) an EL-4 tumor cell armed Bi-Mab anti-gp115:anti-4-1BB

used for the stimulation of T cells. Page 4. Further, the Examiner acknowledges that the specification is enabling for a representative vaccine/composition comprising CD28:gp115 Bi-Mab used for treating human heptatocellular carcinoma and colon cancer. Page 4. The Examiner also acknowledges that the specification does disclose that the claimed binding sites can be directed towards such representatives as CD28, 4-1BB, CTLA-4 or ICAM-1, ICAM-2, ICAM-3, LFA-1, LFA-2, VLA-1 VCAM-1 B7-1, B7-2 and other cell adhesion proteins and other cell adhesion proteins and other cell surface proteins that can activate T cell costimulatory pathways through T cell surface proteins, antigens, fatty acids, lipids, steroids and sugars that can costimulate these effector cells' functions to destroy target cells, and the Examiner acknowledges that the specification further discloses that representatives of the bridge molecules described therein may include bispecific monoclonal antibodies, fusion proteins, organic polymers and other various hybrids. The

Examiner again acknowledges that representatives of the described bispecific antibodies may include CD28:gp55, CD28:gp95, CD28:gp115 and CD28:gp210. The Examiner also acknowledges that the specification discloses that representative target diseased cells may include brain tumors, pancreatic tumors, lung tumors, colon tumors, liver tumors, gynecologic tumors, prostate tumors, bladder tumors, skin tumors, soft tissue tumors, and in particular human hepatocellular carcinoma and colon cancer.

Hence, since the PTO has itself recognized that limiting an applicant to the preferred materials in absence of limiting prior art does not serve the constitutional purpose of promoting progress in the useful arts, (M.P.E.P. §2164.08(c).) Applicant respectfully requests that the rejection be withdrawn.

## III. The Section 112, Second Paragraph, Rejections of Paragraph 7, Pages 5 to 6

Claims 1 to 4 stand rejected under 35 USC §112, second paragraph, as being indefinite for allegedly failing to particularly point out and distinctly claim the subject matter.

A. The Examiner alleges that claims 1 and 3 lack antecedent basis and are therefore rejected. In order to expedite prosecution and advance the case towards allowance, Applicant has amended said claims to provide the appropriate antecedent basis. This amendment is not related to issues of patentability and, therefore, should not be construed as limiting the appropriate scope of protection provided under the doctrine of equivalents. In light of this amendment the Examiner's objection is now moot, and withdrawal of the rejection is respectfully requested.

B. The Examiner further alleges that claims 1 and 3 are indefinite because they clear as to what is being used to treat the target diseased cells claimed therein.

Applicant respectfully submits that the claim is clear and definite in light of the specification. It is well established that claims are to be understood with recourse to the specification. The specification clearly states on page 16, lines 24 – 27, that the treatment in question is to take place with the use of "cytokines or other factors capable of inducing the desired amplification" and/or the transfer of "MHC genes, adhesion molecules genes, cytokine genes and/or MHC, adhesion molecule and cytokine gene transcription activators or enhancers." Given the above, Applicant respectfully request the withdrawal of the rejection.

## IV. Other Informal Matters

A. Claim 4 is objected to as being the exact duplicate of claim 2.

In order to expedite prosecution and advance the case towards allowance, Applicant has amended said claim to depend on Claim 3 rather than claim 1. This amendment is not related to issues of patentability and, therefore, should not be construed as limiting the appropriate scope of protection provided under the doctrine of equivalents. In light of this amendment the Examiner's objection is now moot, and withdrawal of the rejection is respectfully requested.

B. The disclosure is objected to because claim 4 does not have a period.

In order to expedite prosecution and advance the case towards allowance, Applicant has amended said claim by adding a period. This amendment is not related to issues of patentability and, therefore, should not be construed as limiting the appropriate scope of protection provided under the doctrine of equivalents. In light of this amendment the Examiner's objection is now moot, and withdrawal of the rejection is respectfully requested.

## V. The Section 102 (a) Rejection of Paragraph 11, Pages 6 to 7

Claims 1-4 and 6 stand rejected under 35 USC §102 (a) as allegedly anticipated by *Shi et al.* Proc. Amer. Assoc. Cancer Res. March 1996, Volume 37, page 480, Abstract No. 3278 ("Shi et al.").

Applicant respectfully traverses this rejection. Applicant submits that the *Shi et al.* article is not properly citable as prior art under § 102(a). Section 102(a) requires that if "the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the thereof by the applicant for patent".

Since the present applicant is a co-author of the *Shi et al.* reference, clearly the present applicant had conceived of the present invention at least as early as the date of submission of the *Shi et al.* article. Thus, Applicant submits that is not prior art under § 102(a). As the Federal Circuit stated *In re Katz*:

> "Ones own work is not prior art under § 102(a) even though it has been disclosed to the public in a manner or form which otherwise would fall under § 102(a). Disclosure to the public of one's own work constitutes a bar to the grant of a patent claiming the subject matter so disclosed...only when the disclosure occurred more than one year prior to the date of the application." *In re Katz*, 687 F.2d 450 (CCPA 1982).

Hence, the *Shi et al.* article, of which the present applicant is a co-author, can not anticipate the present application.

In view of the above, Applicant respectfully requests that the Examiner reconsider and withdraw this rejection.

## VI. OBVIOUSNESS TYPE DOUBLE PATENTING

Claim 6 stands rejected on provisional double patenting grounds as allegedly claiming the same invention as that of the copending and commonly owned Application No. 08/872,527.

Applicant notes that no claims have been allowed in either the present application or USSN 08/872,257.

Applicant will deal appropriately with this rejection when there is an allowance of claims in one of the applications.

## CONCLUSION

Applicant submits that all the present rejections have been traversed. Accordingly, the application is now in condition for allowance and a notice to that effect is respectfully requested.

Please charge the three-month extension fee of the amount of $445.00 to our Deposit Account No. 12-2475.

If the enclosed fee is incorrect, or if any other fee is due in connection with this amendment, please charge Deposit Account No. 12-2475 for the appropriate amount or credit any overpayment.

Respectfully submitted,

**LYON & LYON LLP**

Dated: March 13, 2001

By: _____
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**Serial Number No. 09/216,062**

**Clean Claim Sheets**

1. (Amended) A method of preparing a pharmaceutical composition for stimulating T cell immune response to nonimmunogenic or low immunogenic diseased cells, in a patient mammal, comprising the steps of:

(a) providing a plurality of an autologous target diseased cell;

(b) treating said target diseased cell to increase the levels of one or more primary and costimulatory T cell activation molecules in said target diseased cell;

(c) providing a plurality of a bridge molecule comprising one or more binding sites for one or more costimulatory molecules on the surface of T cells in said patient mammal;

(d) attaching said bridge molecule to said target diseased cell; and

(e) thereafter collecting a pharmaceutically effective amount of said target diseased cell with said bridge molecule attached thereto; wherein said steps (c) and (d) are performed either before or after said step (b).

2. The method of claim 1, wherein said collecting in step (e) comprises the step of removing said bridge molecule not attached to said target diseased cell.

3. (Amended) A method of preparing a therapeutic vaccine for treating a patient mammal having nonimmunogenic or low immunogenic diseased cells, comprising the steps of:

(a) providing a plurality of an autologous target diseased cell;

(b) treating said target diseased cell to increase the levels of one or more primary and costimulatory T cell activation molecules in said target diseased cell;

(c) providing a plurality of a bridge molecule comprising one or more binding sites for one or more costimulatory molecules on the surface of T cells in said patient mammal;

(d) attaching said bridge molecule to said target diseased cell; and

(e) thereafter collecting a pharmaceutically effective amount of said target diseased cell with said bridge molecule attached thereto; wherein said steps (c) and (d) are performed either before or after said step (b).

4. (Amended) The method of claim 3, wherein said collecting in step (e) comprises the step of removing said bridge molecule not attached to said target diseased cell.

6. An immunogenic composition useful for treating a patient mammal having diseased cells, comprising:

a pharmaceutically effective amount of an isolated autologous target diseased cell which expresses one or more primary and costimulatory T cell activation molecules at a level higher than that in said diseased cells in said patient mammal; and

a pharmaceutically effective amount of a bridge molecule capable of stimulating T cell activation comprising one or more binding sites for one or more costimulatory molecules on the surface of T cells in said patient mammal, wherein said bridge molecule is attached to said target diseased cell and said immunogenic composition is substantially free of said bridge molecule not attached to said isolated autologous target diseased cell.

23. (new) The method of claim 1, wherein said target diseased cell is selected from the group comprising of brain tumors, pancreatic tumors, lung tumors, colon tumors, liver tumors, breast tumors, gynecologic tumors, prostate tumors, bladder tumors, skin tumors and soft tissue tumors.

24. (new) The method of claim 23, wherein said target cell comprising hepatocellular carcinoma.

25. (new) The method of claim 23, wherein said target cell comprises colon carcinoma.

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26. (new) The method of claim 23, wherein said target cell comprises lymphoma.

27. (new) The method of claim 23, wherein said treating is with cytokines.

28. (new) The method of claim 23, wherein said bridge molecules are selected from the group consisting of bispecific monoclonal antibodies, fusion proteins, organic polymers, and hybrids of chemical and biochemical materials.

29. (new) The method of claim 28, wherein said bridge molecules comprise bispecific monoclonal antibodies.

30. (new) The method of claim 29, wherein said bispecific monoclonal antibodies comprise CD:28gp55, CD28:gp95, CD28:gp115 and CD28:gp210.

31. (new) The method of claim 1, wherein said costimulatory molecules are selected from the group consisting of CD-28, 4-1BB and CTLA-4.

32. (new) The method of claim 1, wherein said binding sites are selected from the group consisting of CD28, 4-1BB, CTLA-4, ICAM-1, ICAM-2, ICAM-3, LFA-1, LFA-2, VLA-1, VCAM-1, B7-1 and B7-2.

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33. (new) The method of claim 32, wherein said binding sites are selected from the group consisting of cell adhesion proteins, cell surface proteins, antigens, fatty acids, lipids, steroids and sugars that can activate T cell costimulatory pathways.

34. (new) The method of claim 3, wherein said target diseased cell is selected from the group consisting of brain tumors, pancreatic tumors, lung tumors, colon tumors, liver tumors, breast tumors, gynecologic tumors, prostate tumors, bladder tumors, skin tumors and soft tissue tumors.

35. (new) The method of claim 34, wherein said target cell comprises hepatocellular carcinoma.

36. (new) The method of claim 34, wherein said target cell comprises colon carcinoma.

37. (new) The method of claim 34, wherein said target cell comprises lymphoma.

38. (new) The method of claim 3, wherein said treating is with cytokines.

39. (new) The method of claim 3, wherein said bridge molecules are selected from the group consisting of bispecific monoclonal antibodies, fusion proteins, organic polymers, and hybrids of chemical and biochemical materials.

40. (new) The method of claim 39, wherein said bridge molecules comprise bispecific monoclonal antibodies.

41. (new) The method of claim 40, wherein said bispecific monoclonal antibodies comprise CD:28gp55, CD28:gp95, CD28:gp115 and CD28:gp210.

42. (new) The method of claim 3, wherein said costimulatory molecules are selected from the group consisting of CD-28, 4-1BB and CTLA-4.

43. (new) The method of claim 3, wherein said binding sites are selected from the group consisting of CD28, 4-1BB, CTLA-4, ICAM-1, ICAM-2, ICAM-3, LFA-1, LFA-2, VLA-1, VCAM-1, B7-1 and B7-2.

44. (new) The method of claim 43, wherein said binding sites are selected from the group consisting of cell adhesion proteins, cell surface proteins, antigens, fatty acids, lipids, steroids and sugars that can activate T cell costimulatory pathways.

**Serial Number No. 09/216,062**

**Claim Sheets Marked up to Show Changes**

1. (Amended) A method of preparing a pharmaceutical composition for stimulating T cell immune response to nonimmunogenic or low immunogenic diseased cells, in a patient mammal, comprising the steps of:

(a) providing a plurality of an autologous target diseased cell;

(b) treating said target diseased cell to increase the levels of one or more primary and costimulatory T cell activation molecules in said target diseased cell;

(c) providing a plurality of a bridge molecule comprising one or more binding sites for one or more costimulatory molecules on the surface of T cells in said patient mammal;

(d) attaching said bridge molecule to said target diseased cell; and

(e) thereafter collecting a pharmaceutically effective amount of said target diseased cell with said bridge molecule attached thereto; wherein said steps (c) and (d) are performed either before or after said step (b).

3. (Amended) A method of preparing a therapeutic vaccine for treating a [host] patient mammal having nonimmunogenic or low immunogenic diseased cells, comprising the steps of:

(a) providing a plurality of an autologous target diseased cell;

(b) treating said target diseased cell to increase the levels of one or more primary and costimulatory T cell activation molecules in said target diseased cell;

(c) providing a plurality of a bridge molecule comprising one or more binding sites for one or more costimulatory molecules on the surface of T cells in said patient mammal;

(d) attaching said bridge molecule to said target diseased cell; and

(e) thereafter collecting a pharmaceutically effective amount of said target diseased cell with said bridge molecule attached thereto; wherein said steps (c) and (d) are performed either before or after said step (b).

4. (Amended) The method of claim [1] 3, wherein said collecting in step (e) comprises the step of removing said bridge molecule not attached to said target diseased cell.